

GENE EXPRESSION BY POSITIVE FEEDBACK ACTIVATION OF A CELL TYPE-SPECIFIC PROMOTER

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Abstract

A nucleic acid construct is described which provides cell type-specific expression of a therapeutic transgene. The construct utilizes a cell type-specific promoter which drives expression of the transgene. A positive feedback loop is introduced through the addition of a amplification promoter element operably linked to the therapeutic transgene and by providing, either as part of the same construct, or in a different construct, a transcription activator for activating the amplification promoter element. In one embodiment, the amplification promoter element is a heat shock response element (HSE) and the transcription activator is HSF-1. The construct enables functional targeting of a therapeutic gene while avoiding undesirable effects in non-targeted cells, by combining sufficiently high-level expression to promote a desirable therapeutic outcome with exceptional tissue specificity. A series of promoter elements, constructs, vectors, and therapeutic approaches is presented for gene therapy of tumors such as melanoma and other genetic diseases.

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